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EXAMINER	
BORGEEST, CHRISTINA M	
ART UNIT	**PAPER NUMBER**
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/680,087	LAMPING ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *21,22,25,26 and 30-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,23,24 and 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-20, 23-24 and 27-29) drawn to methods of detecting disease comprising obtaining a biological sample from a patient, determining the concentration of at least one VGF protein or VGFARP peptide in said sample and comparing the concentration, wherein a difference between the concentration of the VGF protein or VGF ARP peptide in the control sample is indicative of disease, in the reply filed on 12 December 2006 is acknowledged. In addition, the election of species VGF-peptide sequence SEQ ID NO: 11 is also acknowledged.

Claims 21-22, 25-26 and 30-57 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12 December 2006.

Claims 1-20, 23-24 and 27-29 will be examined insomuch as they are drawn to methods of detecting disease comprising obtaining a biological sample from a patient, determining the concentration of at least one VGF protein or VGFARP peptide, which is SEQ ID NO: 11, in said sample and comparing the concentration, wherein a difference between the concentration of the VGF protein or VGF ARP peptide in the control sample is indicative of disease.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because the instant application is a continuation in part (CIP) of PCT DE02/01376. Since PCT DE02/01376, as filed designated the US, then it is proper for Applicants to file a CIP under 35 U.S.C. 120 before the PCT which Applicants did. However, the declaration is incorrect by claiming foreign priority to the PCT under 35 U.S.C. 119. Correction of the declaration is necessary to overcome this objection.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Germany on 6 April 2001 (101 17 431.4). It is noted, however, that applicant has not filed a certified copy of 101 17 431.4 application as required by 35 U.S.C. 119(b). In addition, although Applicant has indicated that the instant application is a continuation-in-part of PCT/DE02/01736, this document is in German, therefore it could not be determined whether the PCT contained enabling support for the instant specification in the manner required for the claim to benefit. Therefore, priority to these documents is denied, and the effective filing date is **6 October 2003**.

Claim Objections

Claims 2 and 3 objected to because of the following informalities: they recite non-elected species. Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20, 23, 24 and 27-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting Alzheimer's (or other types of dementia indicated in the prior art as being enabled) comprising measuring the VGF peptide having the sequence set forth in SEQ ID NO: 11 (VGFARP-13) in the cerebrospinal fluid of patients, wherein lower levels of said VGF peptide relative to controls is indicative of Alzheimer's, wherein said method is carried out in combination with other diagnostic methods for Alzheimer's, does not reasonably provide enablement for the claims as broadly recited. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the

existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The first issue is breadth. The claims recited a method for "detecting a chronic dementia disease or a predisposition to a chronic dementia disease" or a "neurological disease." These terms are extremely broad, encompassing, stroke, vascular dementia, Alzheimer's, Niemann-Pick disease, Kreutzfeld-Jakob disease (a.k.a. mad cow disease), ALS, schizophrenia to name a very few, and there is no evidence in the specification or the literature that the claims could detect any dementia or neurological disease. In addition, the claims recite that the methods are carried out comprising obtaining a "biological sample", which encompasses any possible tissue or body fluid, including those where there is no VGF. Claim 9 recites that the "method is used to determine a parameter...", which is broad, because it is not clear how the parameter will be determined, and encompasses thought processes, as well as assays. Furthermore, the claims recite, either implicitly or explicity, that the difference in concentration in VGF protein levels between diseased and control patients can be either an up or a down-regulation, so the claims encompass any change in VGF levels with respect to controls for the diagnosis of any dementia or neurological disease. Finally, with respect to diagnosing a disease or a predisposition to a disease, both normal controls and those with Alzheimer's have detectable levels of VGF (see Figure 6R), and it is not clear from the teachings in the specification or the literature what the level of protein must be (i.e. how high or low) before a diagnosis can be made.

The nature of the invention is complex, namely diagnosis of dementia and/or neurological disease. The claims encompass antemortem diagnosis Alzheimer's (the working examples are drawn to diagnosis of Alzheimer's) the level of predictability in the art is low with respect to reliable antemortem diagnosis of Alzheimer's. For instance, see Bennet et al. (Dis Mon. 1992, 38: 1-64—whole document, especially pages 8-9), in which the complexity and unpredictability of antemortem diagnosis of Alzheimer's is taught. In addition, with regard to the levels of VGF indicative of disease, there is evidence in the literature that higher levels of VGF relative to controls are found in the brain tissue from individuals with schizophrenia (Huang et al. PloS Medicine. 2006; 11: 2145-2158—see p. 2151, left column, 2nd paragraph). The instant specification and several other papers (Carrette et al. Proteomics 2003; 3: 1486-1494; Selle et al. Combinatorial Chemistry & High Throughput Screening, 2005, 801-806; Ruetschi et al. Experimental Neurology. 205; 196: 273-281) have demonstrated that lower levels of VGF proteins are found in the CSF of patients with Alzheimer's disease and frontotemporal dementia. The evidence from the specification and the prior art suggests to the person of skill in the art that the higher levels of VGF measured in the CSF might be useful in aiding a diagnosis of schizophrenia and that lower levels of VGF measured in the CSF might be useful in aiding the diagnosis of Alzheimer's or frontotemporal dementia, however, not for the claims as broadly recited. See MPEP 2164.08; questions of enablement are evaluated against the claimed subject matter, i.e., the focus of the examination inquiry is whether everything within the scope of the claim is enabled. In biotechnology in general, and in diagnosis of dementia and/or

neurological disease in particular, there is a relatively incomplete understanding in the field involved, and the lack of a reasonable correlation between the narrow disclosure in the specification and the art (i.e., VGF may be a biomarker for disease in schizophrenia, Alzheimer's and frontotemporal dementia), and the broad scope of protection sought in the claims (i.e., diagnosis of any type of dementia or neurological disease measuring VGF in any body tissue or fluid without a recitation of whether there is an up- or a down-regulation in diseased individuals with respect to controls), a rejection under 35 U.S.C. 112, first paragraph for lack of enablement is appropriate.

Due to the large quantity of experimentation necessary to establish a nexus between VGF levels and vast types of dementia and neurological diseases encompassed by the claims, the lack of direction/guidance presented in the specification regarding and the absence of working examples directed to the same, the complex nature of the invention, and the breadth of the claims which fail to recite limitations the type of dementia or neurological disease, whether and how much VGF must be up- or down-regulated to be indicative of a particular type of disease, establishing which bodily fluids and tissues that could constitute a suitable "biological sample" to carry out the claimed methods, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 13, 14, 15, 16, 20, 23, 24, 27, 28, 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Alberini et al. (WO 01/74298, published 11 October 2001), which is identical to the pre-grant publication, 20030166555, filed 20 September 2002.

The claims are drawn to methods of detecting a chronic dementia or neurological disease comprising obtaining a biological sample, determining a concentration of at least one VGF protein or VGFARP peptide in said sample, comparing the concentration of the same protein or peptide in a control sample, wherein a difference (either up or down-regulation) between the concentration of the VGF protein or VGFARP peptide in the biological sample compared to the concentration of the VGF protein or VGFARP peptide in the control sample is indicative of chronic dementia, predisposition to a chronic dementia or a neurological disease, wherein the VGFARP peptide is SEQ ID NO: 11, wherein the VGF protein or VGFARP peptide is chemically or post-translationally modified, wherein the dementia Alzheimer's or a related neurological disease, wherein the biological sample is a tissue homogenate, wherein the VGF protein or VGFARP peptide is identified with enzyme linked

immunosorbent assay (ELISA), a radioimmunoassay or western blot, wherein the substance that binds to the VGF protein or VGFARP peptide is an antibody, wherein said methods are used to monitor the efficacy of therapy for a neurological disease, or stratifying patients who are suitable for therapies or clinical studies of neurological diseases.

Alberini et al. (WO 01/74298) teach diagnostic and prognostic assays comprising if a subject is at risk for a disorder characterized deterioration of memory consolidation (i.e., memory disorder; see p. 40, last paragraph; p. 43-45, whole pages) using antibodies to long term memory or LTM proteins, and VGF is defined as one of these proteins (see p. 6, last paragraph to p. 7, 1st paragraph; p. 24, 1st paragraph). One such memory disorder contemplated in their application is Alzheimer's (see p. 7, 3rd paragraph; p. 39, 2nd paragraph). Alberini et al. further teach that "antibodies directed against wild type or mutant LTM proteins, which are discussed, above, may also be used in disease diagnostics and prognostics. "Such diagnostic methods, may be used to detect abnormalities in the level of LTM protein expression," in tissue (see p. 43-45, whole pages). Different types of immunoassays are contemplated, including radioimmunoassay, ELISA and western blot (see p. 43-45, whole pages). In addition, Alberini et al. contemplate that the LTM proteins could be chemically and/or post-translationally modified (see p. 41, 1st paragraph; also see for example, p. 43, 1st paragraph paragraph, "structural differences may include, for example, differences in the size, electronegativity, orantigenicity [sic] of the mutant LTM protein relative to the normal LTM protein"), thus meeting the limitations of claims 4-5. In addition, because

the methods by Alberini contemplate "prognostic and diagnostic" assays, they encompass methods of monitoring the efficacy of therapy and stratifying patients who are suitable for therapies or clinical studies of neurological diseases, because in any clinical setting, diagnosis and prognosis inherently includes monitoring disease course and recommendations for further treatment, thus meeting the limitations of claim 27-28. Finally, Alberini et al. teach the same VGF protein as recited in the claims (i.e., SEQ ID NO: 11):

```
RESULT 5
AAU09069
ID   AAU09069 standard; protein; 616 AA.
XX
AC   AAU09069;
XX
DT   19-DEC-2001  (first entry)
XX
DE   Human neuroendocrine VGF.
XX
KW   Human; long-term memory protein; LTM; neuroendocrine VGF; neuroleptic;
KW   anticonvulsant; nootropic; neuroprotective; C/EBPbeta; cerebroprotective;
KW   drug discovery; therapeutic profiling; learning disability;
KW   memory impairment; brain injury; epilepsy; mental retardation;
KW   senile dementia; Alzheimer's disease.
XX
OS   Homo sapiens.
XX
PN   WO200174298-A2.
XX
PD   11-OCT-2001.
XX
PF   02-APR-2001; 2001WO-US010661.
XX
PR   31-MAR-2000; 2000US-0193614P.
XX
PA   (UYBR-) UNIV BROWN RESEACH FOUND.
PA   (HUGH-) HUGHES HOWARD MED INST.
XX
PI   Alberini CM,  Bear MF;
XX
DR   WPI; 2001-626335/72.
DR   N-PSDB; AAS14697.
XX
PT   Regulating memory consolidation in an animal comprising treating with an
PT   agent that modulates activity of one or more genes from zif268, insulin-
PT   like growth factor, glutamate receptor 2, c/EBPbeta and VGF.
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XX
PS   Disclosure; Page 98-100; 100pp; English.
XX
CC   The invention relates to modulating long term memory consolidation in an
CC   animal comprises treating with an agent that modulates the activity of
CC   one or more of genes from zif268, insulin-like growth factor (IGF),
CC   glutamate receptor 1 (GluR1), glutamate receptor 2 (GluR2), c/EBPbeta and
CC   neuroendocrine VGF (neurotropin-inducible gene). The method is useful for
CC   identifying an agent which modulates memory consolidation. The method is
CC   useful for conducting a drug and/or target discovery business, which
CC   comprises conducting therapeutic profiling of the agents (or their
CC   analogues) identified, for efficacy and toxicity in animals, and
CC   formulating a pharmaceutical preparation including one or more agents
CC   identified as having an acceptable therapeutic profile and/or licensing
CC   to a third party the rights for further drug development of the
CC   identified agents. The method of conducting drug discovery business
CC   further comprises an additional step of establishing a distribution
CC   system for distributing the preparation for sale and may optionally
CC   include establishing a sales group for marketing the preparation. A
CC   pharmaceutical composition containing the agent is useful for enhancing
CC   memory consolidation in an animal, or for augmenting learning and memory,
CC   or otherwise for enhancing the functional performance of central nervous
CC   system neurons, where the agent is a cAMP elevating agent (agonist)
CC   preferably a cAMP analogue or cAMP phosphodiesterase inhibitor, which
CC   activates adenylate cyclase. The composition is useful for treating
CC   diseases associated with learning disabilities, memory impairment e.g.
CC   due to toxicant exposure, brain injury, epilepsy, mental retardation in
CC   children and senile dementia, including Alzheimer's disease. The present
CC   sequence represents human neuroendocrine VGF
XX
SQ   Sequence 616 AA;

  Query Match             100.0%;  Score 300;  DB 4;  Length 616;
  Best Local Similarity   100.0%;  Pred. No. 1.7e-27;
  Matches   59;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 SQEETPGHRRKEAEGTEEGGEEEDDEEMDPQTIDSLIELSTKLHLPADDVVSIIEEVEE 59
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 SQEETPGHRRKEAEGTEEGGEEEDDEEMDPQTIDSLIELSTKLHLPADDVVSIIEEVEE 479
```

Thus, the claims do not contribute anything over the prior art.

Claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 13, 14, 15, 16, 20, 23, 24, 27, 28, 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Lo et al., US Patent No. 6,277,974, which was issued 21 August 2001 and filed 14 December 1999.

A discussion of what is encompassed by the claims can be found in the rejection immediately preceding. The '974 patent teaches methods of diagnosis of conditions, disorders, or diseases involving cell death, including, but not limited to, neurological disorders such as stroke, using "protective sequences", their products (i.e., proteins), or antibodies that may be used diagnostically, and methods for the diagnostic monitoring of patients undergoing clinical evaluation for the treatment of conditions or disorders involving cell death, for monitoring the efficacy of compounds in clinical trials and for identifying subjects who may be predisposed to such conditions, disorders, or diseases involving cell death (see column 2, lines 10-45). One of the "protective sequences" taught in the '974 patent is CNI-00724, which has 94% identity to VGF nerve growth factor mRNA (see column 23, Table 11, lines 20-28; column 76, lines 45-60). The '974 patent also contemplates chemical or post-translational modification of the proteins, see for example, column 38, lines 63-67 to column 39, lines 1-4. In addition to stroke, the '974 patent contemplates other diseases associated with cell death, including Alzheimer's (see column 37, lines 11-29):

> In addition to stroke, a variety of other conditions, disorders, and diseases lead to the activation of the same biochemical cascades which lead to neuronal cell death in stroke. There is growing evidence that numerous other disease states that induce cell death programs are related to those induced by stroke. Cell death programs have been increasingly implicated in Alzheimer's disease, a well-known neurodegenerative condition which leads to substantial loss of specific neuronal populations in the neocortex and hippocampus. Vascular dementia (multi-infarct dementia) is another disorder in which stroke-like cell death pathways are active. In vascular dementia, a repetitive process of small blood vessel diseases induces regional brain cell death, leading to a progressive loss of cognitive abilities. A partial list of other brain diseases which activate brain cell death pathways similar to those observed in stroke include, but are not

limited to, Parkinson's disease, traumatic injury, Down's syndrome, Huntington's disease, HIV infection and intracranial infections.

The '974 patent teaches the protective sequences can be used to diagnose, monitor therapy and that various immunoassays can be employed (i.e., antibodies can be used to detect the proteins—see column 58, lines 65-67 to column 59, 60 and 61—entire columns):

> Protective sequence products (i.e. proteins) of the invention, including both wild-type and mutant protective sequence products, conserved variants and polypeptide fragments thereof...may be detected using antibodies which are directed against such gene products. Such antibodies...may thereby be used as diagnostics and prognostics for a condition, disorder, or disease involving cell death. Such methods may be used to detect abnormalities in the level of protective sequence expression or of protective sequence product synthesis, or abnormalities in the structure, temporal expression and/or physical location of protective sequence product. The antibodies and immunoassay methods described herein have, for example, important in vitro applications in assessing the efficacy of treatments for conditions, disorders, or diseases involving cell death...In vitro immunoassays may also be used, for example, to assess the efficacy of cell-based gene therapy for a condition, disorder, or disease involving cell death. Antibodies directed against protective sequence products may be used in vitro to determine, for example, the level of protective sequence expression achieved in cells genetically engineered to produce the protective sequence product. In the case of intracellular protective sequence products, such an assessment is done, preferably, using cell lysates or extracts. Such analysis will allow for a determination of the number of transformed cells necessary to achieve therapeutic efficacy in vivo, as well as optimization of the gene replacement protocol...The protein isolation methods employed herein may, for example, be such as those described [in the prior art]. The isolated cells can be derived from cell culture or from a patient...Preferred diagnostic methods for the detection of protective sequence products, conserved variants or peptide fragments thereof, may involve, for example, immunoassays wherein the protective sequence products or conserved variants or peptide fragments are detected by their interaction with an anti-protective sequence product-specific antibody. Immunoassays for protective sequence products, conserved variants or peptide fragments thereof will typically comprise incubating a sample, such as a biological fluid, a tissue extract, freshly harvested cells or lysates of cells in the

> presence of a detectably labeled antibody capable of identifying the protective sequence product, conserved variants or peptide fragments thereof, and detecting the bound antibody by any of a number of techniques well-known in the art. One of the ways in which the protective sequence product-specific antibody can be detectably labeled is by linking the same to an enzyme, such as for use in an enzyme immunoassay...Detection may be accomplished also using any of a variety of other immunoassays. For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect protective sequence products through the use of a radioimmunoassay (RIA)

Finally, the '974 patent contemplates the diagnosis and treatment in humans, and SEQ ID NO: 11 is a human VGF peptide fragment (see Conclusion). Because the '974 patent teaches diagnosis in humans, their methods inherently encompass the use of the VGF and antibodies to the VGF protein of the instant application. Thus the claims do not teach anything over the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Alberini et al. as applied to claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 13, 14, 15, 16, 20, 23, 24, 27, 28, 29 above, and further in view of Bennet et al. (Dis Mon. 1992, 38: 1-64).

The discussion of the rejection of claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 13, 14, 15, 16, 20, 23, 24, 27, 28, 29 over Alberini et al. and the teachings of Alberini et al. can be found in the paragraphs immediately preceding and are applicable here. Alberini et al. do not specifically teach carrying out the diagnostic methods in combination with other diagnostic methods for chronic dementia diseases. Bennet et al. teach that antemortem diagnosis of Alzheimer's through a combination of clinical history, physical and neurologic examination and laboratory evaluation (see for example, abstract; pps. 8-9). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Alberini et al. by using a combination of diagnostic methods to diagnose Alzheimer's, as taught in Bennet et al. because it is recognized in the art that there is no definitive antemortem diagnostic test for Alzheimer's and that a multi-pronged approach to diagnosis is good clinical practice. For this same reason, a person of ordinary skill in the art would have been motivated to diagnose Alzheimer's using a combination of diagnostic methods. Furthermore, the person of ordinary skill in the art could have reasonably expected success because the

good clinical practice at the time of the invention stipulated that antemortem diagnosis of Alzheimer's be carried out in combination with a variety of diagnostic methods. Thus the claims do not contribute anything non-obvious over the prior art.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lo et al., US Patent No. 6,277,974, as applied to claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 13, 14, 15, 16, 20, 23, 24, 27, 28, 29 above, and further in view of Bennet et al. (Dis Mon. 1992, 38: 1-64). The discussion of the rejection of claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 13, 14, 15, 16, 20, 23, 24, 27, 28, 29 over the '974 patent and the teachings of the '974 patent can be found in the paragraphs immediately preceding and are applicable here. The '974 patent does not specifically teach carrying out the diagnostic methods in combination with other diagnostic methods for chronic dementia diseases. Bennet et al. teach that antemortem diagnosis of Alzheimer's through a combination of clinical history, physical and neurologic examination and laboratory evaluation (see for example, abstract). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of the '974 patent by using a combination of diagnostic methods to diagnose Alzheimer's, as taught in Bennet et al. because it is recognized in the art that there is no definitive antemortem diagnostic test for Alzheimer's and that a multi-pronged approach to diagnosis is good clinical practice. For this same reason, a person of ordinary skill in the art would have been motivated to diagnose Alzheimer's using a combination of diagnostic methods. Furthermore, the person of ordinary skill in the art could have reasonably expected success because the

good clinical practice at the time of the invention stipulated that antemortem diagnosis of Alzheimer's be carried out in combination with a variety of diagnostic methods. Thus the claims do not contribute anything non-obvious over the prior art.

Claims 11, 12, 17, 18, 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alberini et al. (WO 01/74298) as applied to claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 13, 14, 15, 16, 20, 23, 24, 27, 28, 29 above, and further in view of Chambers et al. (J Pathol. 200; 192: 280-288).

The discussion of the rejection of claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 13, 14; 15, 16, 20, 23, 24, 27, 28, 29 over Alberini et al. and the teachings of Alberini et al. can be found in the paragraphs immediately preceding and are applicable here. Alberini et al. do not teach the identification of VGF protein or VGFARP peptide by mass spectrometry, and chromatographic fractionation of the sample using high resolution reverse phase or reverse phase chromatography (HPLC), wherein the biological sample is further subjected to precipitation reactions or liquid phase separations prior to determination. Chambers et al. teach methods of proteomics in the study of disease. Specifically, Chambers et al. teaches that the key steps in proteomics are separation and visualization of the complex protein mixtures, most commonly by 2D-gel electrophoresis and the identification of proteins by mass spectrometry (p. 280, right column, 2nd paragraph). Chambers et al. also teach that proteins can be separated by HPLC. The principle of HPLC in proteomics is taught at p. 281, right column, 3rd- 4th paragraphs (Note that HPLC is liquid phase separation). Finally, although Chambers is

silent on the subject of the theoretical monoisotopic mass peaks recited in claim 12, Alberini et al. teach the detection of human VGF, which is the ***same protein*** as taught in the instant application thus the same polypeptide would by necessity have ***at least one*** of the theoretical monoisotopic mass peaks recited in claim 12. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Alberini et al. by detecting the proteins by mass spectrometry, as taught in Chambers et al. because the proteomics approach allows for the analysis of many cellular proteins at once, thus giving the clinician or researcher "an integrated view of the individual disease processes at the protein level." (See p. 280, left column, 1st two paragraphs). The person of ordinary skill in the art would have been motivated to make these changes for the same reason. See p. 287, left column, last paragraph: "The development of proteomics represents an exciting new way to examine pathological processes at the molecular level and is already leading to improvements in the understanding of many conditions. It will be particularly important to perform proteomic experiments with specific populations of cells, to generate significant information about cell-specific protein expression profiles and how these change in different diseases. As the technology of proteomics analysis continues to improve, it will be possible in the near future to combine genomic and proteomic information to obtain a more comprehensive picture of many pathological conditions." Furthermore, the person of ordinary skill in the art could have reasonably expected success because according to Chambers et al. at p. 28, right column, 1st paragraph, "[the] techniques used are now sufficiently robust and reliable to allow specific questions to be addressed regarding

protein expression in individual diseases. In particular, proteomics offers pathologists the possibility of identifying disease-associated protein markers to assist in diagnosis or prognosis and to select potential targets for specific drug therapy," thus there is a strong suggestion of the general success of using proteomics to detect proteins Thus the claims do not contribute anything non-obvious over the prior art.

Claims 11, 12, 17, 18, 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lo et al., US Patent No. 6,277,974, as applied to claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 13, 14, 15, 16, 20, 23, 24, 27, 28, 29 above, and further in view of Chambers et al (J Pathol. 200; 192: 280-288).

The discussion of the rejection of claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 13, 14, 15, 16, 20, 23, 24, 27, 28, 29 over the '974 patent and the teachings of the '974 patent can be found in the paragraphs immediately preceding and are applicable here. the '974 patent does not teach the identification of VGF protein or VGFARP peptide by mass spectrometry, and chromatographic fractionation of the sample using high resolution reverse phase or reverse phase chromatography (HPLC), wherein the biological sample is further subjected to precipitation reactions or liquid phase separations prior to determination. Chambers et al. teach methods of proteomics in the study of disease. Specifically, Chambers et al. teaches that the key steps in proteomics are separation and visualization of the complex protein mixtures, most commonly by 2D-gel electrophoresis and the identification of proteins by mass spectrometry (p. 280, right column, 2nd paragraph). Chambers et al. also teach that proteins can be separated by

HPLC. The principle of HPLC in proteomics is taught at p. 281, right column, 3rd- 4th paragraphs (Note that HPLC is liquid phase separation). Finally, although Chambers is silent on the subject of the theoretical monoisotopic mass peaks recited in claim 12, the '974 patent teaches the detection of human VGF, which is the ***same protein*** as taught in the instant application thus the same polypeptide would by necessity have ***at least one*** of the theoretical monoisotopic mass peaks recited in claim 12. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of the '974 patent by detecting the proteins by mass spectrometry, as taught in Chambers et al. because the proteomics approach allows for the analysis of many cellular proteins at once, thus giving the clinician or researcher "an integrated view of the individual disease processes at the protein level." (See p. 280, left column, 1st two paragraphs). The person of ordinary skill in the art would have been motivated to make these changes for the same reason. See p. 287, left column, last paragraph: "The development of proteomics represents an exciting new way to examine pathological processes at the molecular level and is already leading to improvements in the understanding of many conditions. It will be particularly important to perform proteomic experiments with specific populations of cells, to generate significant information about cell-specific protein expression profiles and how these change in different diseases. As the technology of proteomics analysis continues to improve, it will be possible in the near future to combine genomic and proteomic information to obtain a more comprehensive picture of many pathological conditions." Furthermore, the person of ordinary skill in the art could have reasonably expected success because according

to Chambers et al. at p. 28, right column, 1st paragraph, "[the] techniques used are now sufficiently robust and reliable to allow specific questions to be addressed regarding protein expression in individual diseases. In particular, proteomics offers pathologists the possibility of identifying disease-associated protein markers to assist in diagnosis or prognosis and to select potential targets for specific drug therapy," thus there is a strong suggestion of the general success of using proteomics to detect proteins Thus the claims do not contribute anything non-obvious over the prior art.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Canu et al. (Genomics. 1997, 45: 443-446) provide evidence that VGF protein recited in the claims is human derived and is a 100% match with SEQ ID NO: 11:

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RESULT 2
VGF_HUMAN
ID   VGF_HUMAN      STANDARD;      PRT;   616 AA.
AC   O15240;
DT   27-MAR-2002, integrated into UniProtKB/Swiss-Prot.
DT   01-JAN-1998, sequence version 1.
DT   27-JUN-2006, entry version 34.
DE   Neurosecretory protein VGF precursor.
GN   Name=VGF;
OS   Homo sapiens (Human).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
OC   Catarrhini; Hominidae; Homo.
OX   NCBI_TaxID=9606;
RN   [1]
RP   NUCLEOTIDE SEQUENCE [GENOMIC DNA].
RC   TISSUE=Placenta;
RX   MEDLINE=98008940; PubMed=9344675; DOI=10.1006/geno.1997.4945;
RA   Canu N., Possenti R., Ricco A.S., Rocchi M., Levi A.;
RT   "Cloning, structural organization analysis and chromosomal assignment
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RT   of the human gene for neurosecretory protein VGF.";
RL   Genomics 45:443-446(1997).
CC   -!- FUNCTION: May be involved in the regulation of cell-cell
CC       interactions or in synatogenesis during the maturation of the
CC       nervous system (By similarity).
CC   -!- SUBCELLULAR LOCATION: Stored in secretory vesicles and then
CC       secreted (By similarity).
CC   -!- TISSUE SPECIFICITY: Expressed in brain.
CC   ---------------------------------------------------------------------
CC   Copyrighted by the UniProt Consortium, see http://www.uniprot.org/terms
CC   Distributed under the Creative Commons Attribution-NoDerivs License
CC   ---------------------------------------------------------------------
DR   EMBL; Y12661; CAA73210.1; -; Genomic_DNA.
DR   Ensembl; ENSG00000128564; Homo sapiens.
DR   HGNC; HGNC:12684; VGF.
DR   MIM; 602186; gene.
DR   GO; GO:0008083; F:growth factor activity; NAS.
KW   Growth factor; Signal.
FT   SIGNAL        1     22       Potential.
FT   CHAIN        23    616       Neurosecretory protein VGF.
FT                                 /FTId=PRO_0000022655.
FT   COMPBIAS    353    447       Asp/Glu-rich (acidic).
SQ   SEQUENCE   616 AA;  67287 MW;  CD1920610201BEB9 CRC64;

  Query Match          100.0%;  Score 300;  DB 1;  Length 616;
  Best Local Similarity  100.0%;  Pred. No. 1e-19;
  Matches   59;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 SQEETPGHRRKEAEGTEEGGEEEDDEEMDPQTIDSLIELSTKLHLPADDVVSIIEEVEE 59
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 SQEETPGHRRKEAEGTEEGGEEEDDEEMDPQTIDSLIELSTKLHLPADDVVSIIEEVEE 479
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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is 571-272-4482. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D. can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Elizabeth C. Kemmerer

Christina Borgeest, Ph.D.

ELIZABETH KEMMERER
PRIMARY EXAMINER